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General introduction

GENERAL INTRODUCTION

The topic of the present thesis, the injury induced stress response, is of interest for physicians already for many centuries. To start, I want to share two statements of famous physicians in the past on the injury induced stress response in their attempt to understand and elucidate its mechanism:

John Hunter, a surgeon, wrote in 1794:

> *"There is a circumstance attending accidental injury which does not belong to disease – namely, that the injury done has in all cases a tendency to produce both the disposition and the means of cure."* [1]

Sir David Cuthbertson, a physician, wrote in 1942:

> *"The physiological response to trauma, in particular its metabolic component, exhibits a complex picture. The period of shock, characterized essentially by depressed cellular metabolism, is initiated by the actual trauma to the cells, direct or indirect. After this the metabolic rate rises with the onset of traumatic inflammation. The diminished and altered metabolism attendant on the tissue damage plays a part in stimulating the repair process."* [1]

Today, the mechanism of the injury induced stress response is still not fully elucidated, but progress has been made on the involvement of the complex neuroendocrine and inflammatory pathways. These insights have boosted the research on perioperative interventions, attempting to modulate the surgical stress response in order to improve outcome after surgery. More work needs to be done in this field as it seems to hold the key to improve surgical outcome. Hence, the aim of the present thesis is to modulate the injury induced stress response and focuses on some specific parts of this stress response, that will be introduced in the next section, titled surgically induced stress response. Then, a brief introduction on nutritional status in surgical patients is given in the section nutritional status and surgical outcome, because this thesis is about modulating the surgical stress response with nutritional interventions. It is followed by an overview on nutritional interventions done to modulate the surgical stress response. In the section studying human metabolism a general description is given of how to look at this kind of research and a more thoroughly description is given of two methods to study metabolism used in this thesis. The elderly surgical patient is described separately, since they differ from the adult surgical patient and are of interest in this thesis. Finally, this general introduction will be concluded with the aims and outline of this thesis.

SURGICALLY INDUCED STRESS RESPONSE

The human body reacts to injury with a defence mechanism attempting to improve conditions necessary for the healing process, that in principle is considered a positive reaction [2]. However, in case of surgery this evolutionary beneficial defence mechanism can be in excess counteracting recovery and leading to increased morbidity and mortality [3].

The surgically induced stress response is mostly referred to as the surgical stress response. The response to surgical trauma is characterized by both a neuroendocrine response, via the hypothalamic-pituitary-adrenal-axis, and an immune-inflammatory response. A close interaction exists between cytokines and the neuroendocrine system [4,5]. This interaction can lead to an off balance immune-inflammatory response. Normally, the immune-inflammatory response is balanced by proinflammatory as well as anti-inflammatory cytokines [4]. Surgical trauma can shift this balance towards an anti-inflammatory cytokine pattern, that is accompanied by a cell-mediated immunodepression [6-9]. This can result in an increased risk of infectious morbidity after surgery [6,8].

The metabolic consequence of the surgical stress response is placing the human body in a catabolic state, that is characterized with hypermetabolism, insulin resistance, proteolysis, and lipolysis [10]. The magnitude of this metabolic derangement is positively related to the magnitude of the surgical trauma endured [11-15]. Postoperative insulin resistance is considered having a central role in this metabolic derangement, since insulin is the main anabolic hormone. Insulin influences not only glucose metabolism, by suppressing gluconeogenesis and enhancing glucose uptake in extra-hepatic tissues, but influences protein and lipid metabolism as well.
Insulin resistance after surgery develops even after minor surgical procedures, such as hernia inguinal repair and laparoscopic cholecystectomy [13]. It is most pronounced on the first postoperative day and continues for at least five days [14]. To return to preoperative insulin sensitivity levels it can easily take several weeks [14].
The pathophysiology of the surgically induced or stress induced insulin resistance is not well understood. At first, stress hormones, especially catecholamines, were considered as having a major part in the development of postoperative insulin resistance [16,17]. However, several studies revealed only a modest rise of these stress hormones after surgery and their elevation was of short duration [14,15,18]. Since postoperative insulin resistance remains at least for days after surgery, it seems unlikely that only shortly elevated stress hormones levels are solely responsible for postoperative insulin resistance. Therefore, other factors are investigated to elucidate the mechanism of

postoperative insulin resistance. A more recent hypothesis is that insulin resistance is related to oxidative stress [19].

Oxidative stress is defined as an imbalance between the production of oxidant species (mainly oxygen derived species) and their neutralization by anti-oxidants. Reactive oxygen species can be derived directly from cellular damage or indirectly via an immune-inflammatory response [20,21]. Therefore, injury inflicted by surgery causes an increase in the production of free radicals as well as an increase in lipid peroxidation, that can lead to a state of oxidative stress [22,23]. Interestingly, reactive oxygen species can promote the gene expression of immune-inflammatory mediators [20,21]. As a consequence, a vicious circle can result between the immune-inflammatory response and reactive oxygen species production.
An oxidative stress state can cause direct cellular injury by damaging lipids, protein and DNA [24]. A result of this damage can vary from just tissue injury to organ dysfunction [25-31]. The human body reacts to oxidative stress with redistribution of anti-oxidants to tissues in need, potentially leading to impaired anti-oxidant stores [23]. The anti-oxidant defence system consists of enzymatic factors, such as superoxide dismutase, catalase and glutathione peroxidase, and non-enzymatic factors, such as alpha-tocopherol, ascorbic acid, beta-carotene and glutathione [24,29,32-37].

It can be concluded that the term surgical stress response is a simplification of a very complex mechanism. In part the surgical stress response seems beneficial for healing and therefore recovery, but in excess it can be detrimental and attempts to modulate this excess seem justified.

NUTRITIONAL STATUS AND SURGICAL OUTCOME

Surgery has a profound metabolic effect, as just described in the previous section. To be able to cope with the surgical stress response, one can imagine that the human body optimally should be in a good condition and preferably stay in a good condition. Already in 1979, Mullen et al. stated that malnourished patients have enhanced risk of a complicated postoperative course compared to well-nourished patients [38]. In the following decades it is consistently confirmed that a poor preoperative nutritional status is detrimental for clinical outcome [39-45].

Malnutrition is a major concern in hospitalized patients. For decades it is reported that approximately one-third to one-half of hospitalized patients are malnourished [46,47]. The surgical patients are no exception and it seems that the occurrence is similar to that of

non-surgical patients. For instance, the incidence of malnutrition in surgical patients, admitted to the Intensive Care Unit (ICU) postoperatively, is similar to the incidence of malnutrition in non-surgical patients admitted to the ICU [39]. A recent observational study in 564.063 hospitalized patients in the Netherlands, revealed in a subgroup of 108.369 surgical patients a prevalence of malnutrition on admission of approximately 10% [48].
A diminished nutritional status or malnutrition can be an inevitable consequence of profound disease [49,50], and therefore can be seen as a marker of severity of disease [50]. Experts of the American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) and European Society of Parenteral and Enteral Nutrition (ESPEN) define malnutrition as 'an acute, subacute or chronic state of nutrition, in which varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function' [50,51].

Many assessment tools are available for screening the nutritional status of a patient, but to date none are advocated as golden standards [52]. The value of 44 used nutritional status assessments have been questioned by Jones. She evaluated their methodology and concluded that none of these assessments satisfied a set of criteria regarding scientific merit [53]. And, even the ESPEN and the A.S.P.E.N. do not advocate an existing screening tool for assessing nutritional status. They have a consensus about the definition of malnutrition, as stated before. This led to the development of criteria which should be met, and the diagnosis malnutrition can be made if the patient exhibit two or more of the following six criteria: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may sometimes mask weight loss and diminished functional status by handgrip strength [54]. The validation of these criteria is still under investigation.

Nutritional support to patients who are malnourished or at risk for malnutrition seems justified in the perioperative period. Koretz et al. presented in a meta-analysis a beneficial effect on postoperative morbidity of enteral nutritional support, showing reduced infectious, intra-abdominal and intrathoracic complications. However, the quality of the included trials in the meta-analysis was low [55]. If nutritional support is really beneficial in these groups of patients in the perioperative period is still unclear.

Reviewing the above, questions remain if the perioperative target should be optimizing nutritional status by nutritional support, attenuating the surgical stress response with nutritional interventions or both.

NUTRITIONAL INTERVENTIONS

Since a couple of decades, various enhanced-recovery-after-surgery or fast-track protocols have been introduced successfully to attenuate the surgical stress response thereby speeding up uncomplicated recovery [56-58]. These multimodal protocols comprehends, among others, numerous modalities to enhance early nutrition after surgery, but also to prevent long-lasting fasting before surgery. Numerous research studies with nutritional interventions were performed to minimize the fasting period perioperatively, thus trying to keep surgical patients in a fed state and thereby aiming to attenuate the surgical stress response. A part of these studies were done with nutritional supplements, with single nutrients or a mixture of nutrients.

Based on clinical evidence, current guidelines advise to grant patients to eat until six hours and to drink clear fluids until two hours before surgery [58,59]. Despite these guidelines, lots of elective surgical patients are still routinely fasted for six to eight hours before surgery and enter the operating room in a postabsorptive state. To prevent patients undergoing elective surgery in an unfed state, carbohydrates can be safely administered as clear fluids until two hours before surgery, because research has shown that longer preoperative fasting does not reduce aspiration, regurgitation or mortality [58,60,61]. Besides being safe to administer, carbohydrate loading has been shown to attenuate the surgery induced insulin resistance [62].

Accumulating clinical evidence has demonstrated that preoperative support with immune-modulating nutrients, a combination of arginine, nucleotides and omega-3 fatty acids, result in a substantial reduction of infectious postoperative complications [63-67]. However, the underlying mechanism of action for this important clinical effect has not completely been elucidated and is still under investigation. These results are mostly obtained from studies in major gastrointestinal surgical patients, but are beginning to come from other surgical patient groups as well [68].

Glutamine is a non-essential amino acid in healthy man, but becomes a conditionally essential amino acid during episodes of catabolic stress, such as following injury [69]. Glutamine is involved in many biological functions [70,71]. It is a nitrogen donor for the synthesis of glutathione, that is a major intracellular anti-oxidant. Also, glutamine is an important fuel for rapidly proliferating cells, such as enterocytes and immunocytes [71,72]. For becoming an essential amino acid during episodes of catabolic stress and having these important biological functions, glutamine deserved and deserves attention in nutritional supplementation.

Glutamine supplementation resulted in profound positive results [68,72]. For instance, in trauma patients, enteral nutritional supplementation with glutamine reduced infectious morbidity possibly by affecting the immune-inflammatory response [73,74]. In another group, of trauma patients, glutamine supplementation prevented a further decrease in insulin sensitivity [75]. Despite these and other positive results of glutamine supplementation, routinely use of glutamine supplementation in surgical patients is still a bridge too far [68,72] and further research is needed to further explore the underlying mechanism of action and to try to confirm these positive results in other surgical patients groups.

Taurine is a semi-essential aminosulfonic acid, that is practically biochemical inert [76,77]. The human body gets taurine by dietary intake via the gut and by endogenous production in the liver [78,79]. However, the human body is mostly dependent on the dietary intake. The kidneys are the main sites of excretion of taurine [80].
Taurine exerts multiple functions in the human body. It is a zwitterion, due to its chemical structure, and has in that way a function in maintaining acid-base homeostasis [72]. Also, taurine has functions as an antioxidant, as an osmoregulator, as an immunomodulator and is involved with bile salt formation [81].
In response to surgery, plasma taurine levels decrease, which suggests an increased metabolic need [82]. Animal and human studies showed that taurine reduced oxidative stress, improved insulin resistance and had a regulating effect in mitochondrial function [83-85]. Taurine supplementation during cardiac surgery reduced lipid peroxidation and cell damage, and improved mitochondrial survival [86]. Supplementing taurine in surgical patients is of interest, since it can be safely administered due to its practical inertness and can possibly reduce postoperative oxidative stress.

As mentioned earlier, due to surgical stress the anti-oxidant defence system might become depleted. Surgical stress decreases the level of the anti-oxidants such as glutathione, ascorbic acid, alpha-tocopherol, beta-carotene, zinc and selenium [29,87-91]. Supplementing these antioxidants may support the anti-oxidant defence system, thereby improving postoperative recovery.

It can be concluded that much research has been done on nutritional supplementation in surgical patients. However, still many research questions on nutritional supplementation in surgical patients remains unanswered and deserve further attention. Being able to attenuate the surgical stress response with nutritional interventions can be an elegant, relatively simple and safe way.

STUDYING HUMAN METABOLISM

Human metabolism is a broad term that entails multiple reactions in the human body to be able to sustain living [92]. Broadly, one can see metabolism in twofold; for anabolism, as biosynthesis of necessary products which requires energy, and for catabolism, to e.g. generate energy and to eliminate waste products. Almost all processes in the human body can be seen as part of this, and studying, even a very small part of this, is also called studying metabolism.

There are numerous methods of studying (parts of) metabolism. A very convenient and commonly used method is the measurement of the substance of interest in the circulatory compartment, thus in blood or parts of blood. It is easy to access and is in most cases economically feasible. However, most parts of metabolism are taking place inside cells, inside and/or between organs. Measuring substances in the circulatory compartment can, can partly or cannot reflect the actual part of metabolism of interest. Studying metabolism inside cells, inside and/or between organs are more challenging for various reasons. For example, it can be quite a challenge to access the adequate material to study, the analytic method used can be quite sophisticated and not easy to access and apply, and the economic aspect can be challenging as well.
Every scientist studying metabolism has to evaluate in advance which method is most suitable, but also taken into account the economic burden. Eventually, the method used can be a comprise between the suitable and the affordable, but with the chosen method one should be able to answer the scientific question at hand.

Aforementioned two methods to study metabolism, the organ flux measurement and the hyperinsulinemic clamp method, will be explained in more detail, since these two methods are used in the present thesis next to the measurements of substances in the circulatory compartment.

Organ flux measurement

Organ flux measurement is a measure of net exchange of a substance across organs. It is calculated using the following equation: net organ flux = ([A] - [V]) * F, where [A] is the arterial plasma concentration, [V] is the venous plasma concentration, and F is the plasma flow through the organ. A negative value indicated release, and a positive value indicated uptake of the substance under investigation by the organ under investigation.

For adequate results of an organ flux it is of utmost importance to have consistent blood sampling of the substance and consistent blood flow measurements [93]. However, it can be quite challenging to access the draining vessels of some organs for blood sampling and blood flow measurements, e.g., the intra-abdominal organs. Therefore, when net organ flux measurements across intra-abdominal organs are wanted, blood sampling and blood flow measurements, e.g., by duplex Doppler ultrasound (DDUS), are performed during surgery and consequently under anesthesia.

Hyperinsulinemic euglycemic clamp method

The gold standard for investigating and quantifying insulin resistance is the “hyperinsulinemic euglycemic clamp”, so called because it measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycaemia. This was first reported by Andres and DeFronzo 1979 [94].
This method has evolved over the years, and one or two-steps techniques (with one or two different insulin infusion rates) can take place. Low dose insulin infusions are more useful for assessing the response of the liver, whereas high dose insulin infusions are useful for assessing peripheral (i.e. muscle and fat) insulin action. A two-step technique takes approximately 5.5 hours.
Also, the basic technique is enhanced by the use of glucose tracers. Glucose is labelled with a stable isotope [6,6-$^{2}H_2$]-glucose. Prior to beginning the hyperinsulinemic period, a tracer infusion (e.g. for two hours) enables one to determine the basal rate of glucose production. During the clamp, the plasma tracer concentrations enable the calculation of whole body insulin stimulated glucose metabolism as well as the production of glucose by the body (i.e. endogenous glucose production) [95].

In practice, through a peripheral vein, insulin is infused at a constant rate. Through a peripheral vein in the opposite hand, blood samples are regularly taken for measurement of basal and steady state conditions. To allow arterialisation, this hand is placed in a heated hand box at 60°C. In order to compensate for the insulin infusion, glucose (e.g. glucose 20%) is infused to maintain blood sugar levels at 5.0 mmol/L. The steady-state rate of glucose infusion at a particular insulin infusion is determined by checking the blood sugar levels regularly according to a predefined schedule (e.g. every five minutes) and adjusting the rate of glucose infusion until a steady-state is reached.

Without using isotopes, the steady-state rate of glucose infusion can determine insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min are not definitive and suggest impaired glucose tolerance, an early sign of insulin resistance.

When using stable isotopes (tracers) insulin resistance, e.g. endogenous glucose production and peripheral glucose uptake, can be calculated using modified forms of the Steele Equations [95].

THE ELDERLY SURGICAL PATIENT

There is a steady grow in the number of elderly surgical patients. In the United Kingdom about a quarter of surgical procedures are done in patients over 75 years old [96]. This correlates with a large amount of surgical procedures.

Elderly patients differ significantly from adult patients. Compared to younger patients, the elderly patient has a reduced adaptive and regenerative capacity [96-98]. This reduction is due to a combination of, among others, age-related physiological decline, multiple comorbidities, polypharmacy and cognitive dysfunction [96,99]. Also, just being older is associated with a diminished nutritional status [100]. This is explained by inadequate intake, less access to adequate nutrition, reduced appetite, chronic disease, medication use and/or reduced psychological condition [101].

Compared to younger surgical patients, elderly surgical patients have a higher risk of developing postoperative morbidity and mortality [96,99]. In elderly hip fracture patients it has been shown that mainly patient case-mix variables, e.g., patient characteristics like age and gender, influences postoperative mortality [102-104]. And, increased complexity in comorbidities over time have been shown in a recent observational study in elderly surgical patients [99], which negatively influences postoperative outcome [105]. Fortunately, improved perioperative plans have been able to reduce postoperative morbidity and mortality in elderly surgical patients [99]. We are still at the beginning of looking separately at the group of elderly surgical patients. Therefore, it remains a challenge to adequately adjust perioperative care and especially postoperative recovery to the elderly surgical patient.

AIMS AND OUTLINE OF THE THESIS

The major aim of this thesis was to attenuate the surgical stress response with nutritional interventions containing anti-oxidative supplements. The surgical procedure in combination with the patient population for the different studies, were chosen because of the expected profound surgical stress response. This thesis reports on multiple studies with diverse anti-oxidative nutritional supplements, such as a single nutrient supplement and two mixtures of nutritional supplements, which were all given via the enteral route. Various aspects of the surgical stress response were studied, such as the immuno-inflammatory response, the oxidative stress response and surgery induced insulin resistance.

Since single nutrient supplements, like selenium and glutamine, had proven to be beneficial in several patient groups [29,70,73,106-108], we expected a mixture of nutritional supplements to have the same and possibly additional positive effects after surgery. Therefore, we explored an enteral supplement mixture with anti-oxidants in major upper gastro-intestinal tract surgery patients. In a randomized controlled setting the supplement was given via jejunostomy from the first postoperative day for almost a week. In **chapter 2** the effect of this supplement on circulating factors of the anti-oxidant defence system and markers of oxidative stress was investigated. And, in **chapter 3** the effect of this supplement on circulating levels of immuno-inflammatory markers was investigated.

Numerous studies by a Swedish research team revealed that surgery induced insulin resistance can be reduced by a preoperatively given carbohydrate rich drink [62,109-111]. This knowledge, combined with research data revealing an association between insulin resistance and oxidative stress [19,112,113], and promising results of anti-oxidative agents that maintained insulin sensitivity [83,114,115], lead to another study. In **chapter 4** we report on a placebo controlled trial with a preoperative drink containing carbohydrates, glutamine and antioxidants in rectal cancer surgery patients.

For years our research team has been interested in the amino acid taurine, which is a strong anti-oxidant. Taurine is practically inert, and has therefore a high potential as a supplement. Also, taurine plasma levels decrease in response to pathological conditions, such as surgery, which indicates an increased metabolic need [77,82]. Before starting supplementing taurine, we studied human taurine metabolism in **chapter 5**, since human data on taurine metabolism were still scarce. Fluxes and fractional extraction rates of the gut, liver and kidneys were studied in patients undergoing partial liver resection.
The number of elderly surgical patients is growing and their nutritional status is often compromised [100,116,117], therefore this population deserves attention of nutritional research teams. Before starting a study in elderly surgical patients, we wanted to gain more knowledge on this population. A systematic review on the elderly surgical patients is found in **chapter 6**. We studied the relationship between their preoperative nutritional status and postoperative outcome.

The gained knowledge on human taurine metabolism and the elderly surgical population lead to a placebo controlled randomized trial in which taurine was given perioperative in elderly hip fracture patients. In **chapter 7** we report on the effect of taurine supplementation on markers of oxidative stress and on outcome parameters, such as morbidity and mortality.

A summary of the investigated topics in this thesis is given in **chapter 8**. In the same chapter conclusions are drawn and future perspectives are given.

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